VERSION WITH MARKINGS TO SHOW CHANGES MADE AUGUST 21, 2002

In the Specification:

The paragraph beginning at page 12, line 15, has been amended as follows:

The present invention will now be described in detail with reference to the following examples and figures [in which].

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 is a schematic presentation of the region between exon 7 and the 3' UTR of the vitamin D receptor genes.

The paragraph beginning at page 13, line 27, has been amended as follows:

We then went on to determine the distribution of fractures in women according to their carrier status for VDR haplotype 1 (Table 3[a]). Significantly more women heterozygous for VDR haplotype 1 had fractures than the women in the reference group and for women homozygous for the VDR haplotype 1 this difference further increased. When women were grouped according to VDR haplotype 2, we observed an under-representation in fracture cases ($p=0.002$) while for VDR haplotype 3 no differences were observed ($p=0.65$; data not shown). Logistic regression analysis showed that women heterozygous for the VDR haplotype 1 had 1.8 times the risk for fractures compared to women in the reference group. This was further increased for women homozygous for the VDR haplotype 1 to 2.6 times the risk for fracture compared to women in the reference group (Table 3[a]). When we analyzed by type of fracture we observed the VDR genotype effect to be similar for vertebral fracture cases ($p=0.07$) and non-vertebral fracture cases ($p=0.04$; data not shown). The relative risk of fracture did not essentially change after adjustment for potential confounding factors such as age, weight, and bone density in the multivariate regression analysis.

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The paragraph beginning on page 14, line 15, has been amended to read as follows:

In this group of women we also determined the distribution of fractures according to COLIA1 genotype (Table 3[b]). In correspondence with what we previously found[10] we observed the COLIA1 T allele to be associated with increased fracture risk, independent of BMD. To assess whether there was interaction between the VDR haplotype effect and the COLIA1 genotype effect on fracture we determined the distribution of fractures according to VDR haplotype 1 in the different COLIA1 genotype groups (Table 4). The distribution of fracture cases according to the VDR genotype did not differ in the group of women with the COLIA1 GG genotype. However, in the COLIA1 risk groups of women with the GT and TT genotypes the distribution of fractures cases was strongly VDR genotype dependent (Table 4[a]). Logistic regression analysis showed that the effect of VDR genotype on fracture risk is absent in women with the COLIA1 GG genotype while the VDR genotype effect is large in the COLIA1 hetereozygous GT and homozygous TT risk group (Table 4[b]). When age, VDR genotype, COLIA1 genotype and fracture were considered together in a multivariate regression model we found that VDR genotype significantly modified the COLIA1 genotype effect ($p=0.03$ for the interaction term). The effect was found to be similar for nonvertebral fracture cases and vertebral fracture cases and when bone density was entered into the model the results did not change indicating the interaction effect to be independent of bone density.

New Tables 1-4 have been added on page 18 prior to the claims.

In the Claims:

Claims 7 and 20 have been canceled, and Claims 1-4, 6, 8, 13, 18, 19, 22-25, and 27-30, have been amended as shown below:

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1. (Amended) A method of determining susceptibility to bone fracture in a subject, said method comprising analyzing genetic material of a subject to determine [the presence of the baT haplotype] which of the B/b, A/a and T/t alleles of the *BsmI, ApaI* and *TaqI* sites of the vitamin D receptor gene are present, wherein [said haplotype is associated with risk of bone fracture] the presence of a haplotype comprising at least one of the b, a and T alleles is indicative of an increased susceptibility to bone fracture.

2. (Amended) A method of determining susceptibility to bone [damage] fracture according to claim 1, said method comprising analysing [the] genetic material of a subject to determine [which of the B/b, A/a and T/t alleles of the *BsmI, ApaI and TaqI* sites] the presence of the baT haplotype of the vitamin D receptor [are present] gene, wherein the presence of said baT haplotype is indicative of an increased susceptibility to bone fracture.

3. (Amended) A method of determining susceptibility to bone fracture according to claim 1 or claim 2, said method further comprising analysing the genetic material of a subject to determine [which] whether an allele of the collagen [II]Iα1 gene is present which is indicative of an increased susceptibility to bone fracture.

4. (Amended) A method of determining susceptibility to bone fracture according to claim 3, said method comprising determining the presence of a G to T polymorphism at the *Sp*1 site of the collagen [II]Iα1 gene, wherein detection of said polymorphism is indicative of an increased susceptibility to bone fracture.

6. (Twice Amended) A method of determining susceptibility to bone fracture according to claim 3, said method further comprising determining the copy number of the B/b, A/a or T/t alleles of the vitamin D receptor gene and/or the S/s allele of the collagen [II]Iα1 gene.

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8. (Amended) A method according to claim 6 comprising comparing the allele(s) present in the genetic material of the subject with genotypes of the vitamin D receptor or collagen [II]Iα1 genes having known degrees of risk of bone fracture.

13. (Twice Amended) A method [according to claim 1, further comprising] of treating [the] a subject to [reducing] reduce the risk of bone fracture comprising analysing genetic material of said subject to determine which of the B/b, A/a and T/t alleles of the *BsmI*, *ApaI* and *TaqI* sites of the vitamin D receptor gene are present, wherein the presence of a haplotype comprising at least one of the b, a and T alleles is indicative of an increased susceptibility to bone fracture, and treating the subject to reduce the risk of bone fracture if the subject has a haplotype comprising at least one of the b, a and T alleles.

18. (Amended) A method of [predicting response of a subject to] formulating a treatment regimen to decrease the risk of bone fracture, said method comprising analysing genetic material of a subject to determine the presence of the baT haplotype of the vitamin D receptor gene, wherein said haplotype is associated with risk of bone fracture, and formulating a treatment regimen to decrease the risk of bone fracture based on said haplotype.

19. (Amended) A method according to claim 18, further comprising determining which allele(s) of the collagen [II]Iα1 gene is/are present.

22. (Amended) [Use of a kit to determine] A method of determining susceptibility to bone fracture in a subject comprising the step of utilizing a kit to determine whether the baT haplotype of the vitamin D receptor gene is present in a subject, wherein said kit [comprising] comprises (i) one or more nucleic acid primer molecules for amplification of a portion of the vitamin D receptor gene, and (ii) means for determining whether the baT haplotype of said gene is present, and wherein presence of the baT haplotype in the subject is indicative of susceptibility to bone fracture.

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23. (Amended) [Use of a kit] The method according to claim 22 further comprising the step of determining which allele of a collagen Iα1 gene is present in the subject, said kit further comprising (i) one or more nucleic acid primer molecules for amplification of a portion of the collagen [II]Iα1 gene and (ii) means for determining which allele of [said] the collagen Iα1 gene is present.

24. (Amended) A kit for determining susceptibility to bone fracture in a subject, said kit comprising (i) one or more nucleic acid primer molecules for amplification of a portion of the vitamin D receptor gene, (ii) means for determining whether the baT haplotype of said gene is present; and (iii) means for indicating correlation between the presence of said [allele(s)] haplotype and risk of bone fracture.

25. (Amended) A kit according to claim 24, said kit further comprising (i) one or more nucleic acid primer molecules for amplification of a portion of the collagen [II]Iα1 gene and (ii) means for determining which allele of [said] the collagen Iα1 gene is present.

27. (Amended) A method according to claim 1, wherein the haplotype [may be] is determined by amplification of a [relevant] portion of the vitamin D receptor gene between exon 7 and the 3' UTR, followed by restriction enzyme digestion; or any other technique suitable for determining the genotype of a subject.

28. (Amended) A method according to claim 2, wherein the haplotype [may be] is determined by amplification of a [relevant] portion of the vitamin D receptor gene between exon 7 and the 3' UTR, followed by restriction enzyme digestion; or any other technique suitable for determining the genotype of a subject.

29. (Amended) A method according to claim 3, wherein the haplotype [may be] is determined by amplification of a [relevant] portion of the vitamin D receptor gene between exon 7 and the 3' UTR, or amplification of the first intron of the collagen [II]Iα1 gene, followed by

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restriction enzyme digestion; or any other technique suitable for determining the genotype of a subject.

30. (Amended) A method according to claim 4, wherein the haplotype [may be] is determined by amplification of a [relevant] portion of the vitamin D receptor gene between exon 7 and the 3' UTR, or amplification of the first intron of the collagen [II]Iα1 gene, followed by restriction enzyme digestion; or any other technique suitable for determining the genotype of a subject.

In the Figures:

After page 26, pages 1/5, 2/5, 3/5 and 4/5 (Tables 1-4) have been deleted and Tables 1-4 have been inserted into the body of the specification after page 18. The page designation 5/5 has been deleted from FIGURE 1.

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